Predictive Models of Acute Mountain Sickness after Rapid Ascent to Various Altitudes

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ABSTRACT

BEIDLEMAN, B. A., H. TIGHIOUART, C. H. SCHMID, C. S. FULCO, and S. R. MUZA. Predictive Models of Acute Mountain Sickness after Rapid Ascent to Various Altitudes. *Med. Sci. Sports Exerc.*, Vol. 45, No. 4, pp. 792–800, 2013. **Purpose**: Despite decades of research, no predictive models of acute mountain sickness (AMS) exist, which identify the time course of AMS severity and prevalence following rapid ascent to various altitudes. **Methods**: Using general linear and logistic mixed models and a comprehensive database, we analyzed 1292 AMS cerebral factor scores in 308 unacclimatized men and women who spent between 4 and 48 h at altitudes ranging from 1659 to 4501 m under experimentally controlled conditions (low and high activity). Covariates included in the analysis were altitude, time at altitude, activity level, age, body mass index, race, sex, and smoking status. **Results**: AMS severity increased ($P < 0.05$) nearly twofold (i.e., 179%) for every 1000-m increase in altitude at 20 h of exposure, peaked between 18 and 22 h of exposure, and returned to initial levels by 48 h of exposure regardless of sex or activity level. Peak AMS severity scores were 38% higher ($P < 0.05$) in men compared with women at 20 h of exposure. High active men and women (>50% of maximal oxygen uptake for >45 min at altitude) demonstrated a 72% increase ($P < 0.05$) in the odds (odds ratio, 1.72; confidence interval, 1.03–3.08) of AMS compared with low active men and women. There was also a tendency ($P = 0.10$) for men to demonstrate greater odds of AMS (odds ratio, 1.65; confidence interval, 0.84–3.25) compared with women. Age, body mass index, race, and smoking status were not significantly associated with AMS. **Conclusions**: These models provide the first quantitative estimates of AMS risk over a wide range of altitudes and time points and suggest that in addition to altitude and time at altitude, high activity increases the risk of developing AMS. In addition, men demonstrated increased severity but not prevalence of AMS. **Key Words**: HYPOXIA, HYPOBARIC HYPOXIA, MIXED MODELS, ALTITUDE, ALTITUDE SICKNESS, UNACCLIMATIZED LOWLANDERS

When civilian and military personnel rapidly ascend to high altitudes (>2500 m), acute mountain sickness (AMS) poses a significant threat to their health and well being (28). AMS is characterized by headache accompanied by other symptoms that may include gastrointestinal distress (e.g., nausea, vomiting, and loss of appetite), fatigue, dizziness, and sleep disturbances (10,13,29). Depending upon individual susceptibility, rate of ascent, and altitude attained, some unacclimatized lowlanders may be completely incapacitated by AMS (10,28). With increased participation in mountain recreation, recent deployment of US troops to Afghanistan, and occupational work sites located at high altitude (25,31,41), the need for a medical planning tool to prevent or effectively manage AMS has become increasingly important (7).

Despite decades of research, no models exist to predict AMS severity and prevalence over a wide range of altitudes and time points in unacclimatized lowlanders after rapid ascent. Many high-altitude destinations can be reached within a day (i.e., rapid ascent) using modern means of transportation, but an AMS prediction model using this high-risk scenario has never been developed. Previous models of AMS have severe limitations because of the use of staged or graded ascents, select study populations (i.e., mountaineers and trekkers), limited range of altitudes and time points, and lack of control for factors such as acclimatization status, ascent rate, medication use, hydration status, and environmental conditions (21,22,33,37,39). Furthermore, none of these models delineate the time course of AMS or predict different grades of AMS severity (i.e., mild, moderate, and severe). The purpose of this study, therefore, was to develop the first predictive models of AMS severity, prevalence, and grade of severity after rapid ascent to various altitudes and delineate the time course of AMS over the first 48 h of exposure. This goal was accomplished using a comprehensive

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14. ABSTRACT

Purpose: Despite decades of research, no predictive models of acute mountain sickness (AMS) exist, which identify the time course of AMS severity and prevalence following rapid ascent to various altitudes. Methods: Using general linear and logistic mixed models and a comprehensive database, we analyzed 1292 AMS cerebral factor scores in 308 unacclimatized men and women who spent between 4 and 48 h at altitudes ranging from 1659 to 4501 m under experimentally controlled conditions (low and high activity). Covariates included in the analysis were altitude, time at altitude, activity level, age, body mass index, race, sex, and smoking status. Results: AMS severity increased (P G 0.05) nearly twofold (i.e., 179%) for every 1000-m increase in altitude at 20 h of exposure, peaked between 18 and 22 h of exposure, and returned to initial levels by 48 h of exposure regardless of sex or activity level. Peak AMS severity scores were 38% higher (P G 0.05) in men compared with women at 20 h of exposure. High active men and women (950% of maximal oxygen uptake for 945 min at altitude) demonstrated a 72% increase (P G 0.05) in the odds (odds ratio, 1.72; confidence interval, 1.03?3.08) of AMS compared with low active men and women. There was also a tendency (P = 0.10) for men to demonstrate greater odds of AMS (odds ratio, 1.65; confidence interval, 0.84?3.25) compared with women. Age, body mass index, race, and smoking status were not significantly associated with AMS. Conclusions: These models provide the first quantitative estimates of AMS risk over a wide range of altitudes and time points and suggest that in addition to altitude and time at altitude, high activity increases the risk of developing AMS. In addition, men demonstrated increased severity but not prevalence of AMS.

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relational mountain medicine database containing individual ascent profiles, demographic and physiologic subject descriptors, and repeated-measures AMS data from 20 carefully conducted experimental studies.

METHODS

Study population. Because of our unique hypobaric chamber and Pikes Peak laboratory facilities, the US Army Research Institute of Environmental Medicine (USARIEM) has been able to collect AMS data (1292 data points) on 308 unacclimatized (no altitude exposure in the previous 3 months) men ($n = 239$) and women ($n = 69$) after rapid ascent (<2 h) and stay at fixed altitudes (1659–4501 m) during the first 48 h of exposure under experimentally controlled conditions (no medication use, adequate hydration, physical activity assessment, controlled temperature, and humidity) to develop predictive models of AMS. Ten studies were conducted in natural altitude conditions (i.e., Pikes Peak, US Air Force Academy), and 10 were conducted in the USARIEM hypobaric chamber. No difference in mean AMS scores existed between natural and hypobaric environments. Ascent times in the hypobaric chamber were more rapid (<15 min) than ascent times in the mountains (<2 h). However, the time variable did not start until arrival at the destination altitude. Only 13% of the volunteers in the database (i.e., 40 volunteers) had any previous exposure to altitude, and all exposures were below 2500 m. In those 40 volunteers, only 20% experienced one or more symptoms of AMS (i.e., eight volunteers). In studies that used medication, only placebo volunteers were included. Recruitment procedures were the same (i.e., both sexes included and age range limited to 18- to 45-yr-olds) for all studies except one study conducted on men only (Special Forces unit) and two studies conducted on women only by design. None of the volunteers participated repeatedly in any of the studies.

Table 1 contains the mean, SD, and range of variables from the study population used to develop AMS severity and prevalence models. Given that sea-level maximal oxygen uptake was assessed in only 191 of the 308 volunteers, this variable was not included in the model because the data set would have been limited. However, maximal oxygen uptake was used to define physical activity levels in volunteers (low, ≤50% sea-level maximal oxygen uptake for ≤45 min upon arrival at altitude, and high, >50% of sea-level maximal oxygen uptake for >45 min upon arrival at altitude). If sea-level maximal oxygen uptake was not measured in a volunteer, activity levels were assigned based on mean values of sea-level maximal oxygen uptake in the Mountain Medicine database for a given age and sex.

Women represented approximately 23% of the data set with an equal distribution (15%–25%) across altitudes. There was also an equal distribution of women (15%–25%) in the four age quartiles (18–23, 24–30, 31–37, and 38–45 yr). In our data set, 62.5% of the data points and 66.9% of the

TABLE 1. Characteristics of unacclimatized men (239) and women ($n = 69$) lowlanders ($n = 308$, 1292 data points) used in the data set.

Variable	Mean	SD	Min	Max
Age (yr)	23.8	5.4	18	45
Weight (kg)	76.3	12.1	47.1	113.3
Height (m)	1.75	0.83	1.47	1.98
BMI (kg·m^{-2})	24.8	2.9	18.3	33.8
Altitude (km)	3.822	0.721	1.659	4.501
Men (%)	77.6			
Maximal oxygen uptake (mL·kg^{-1}·min^{-1}) ($n = 191$)	49.2	8.2	30.0	72.9
Smokers (%)	15.6			
Whites (%)	77.9			
High active (%)	63.6			
AMS (%) (altitude measures)				
Sick	65.3			
Not sick	34.7			
AMS-C (altitude measures)				
Sick	1.378	0.872	0.706	4.876
Not sick	0.129	0.093	0.012	0.451
AMS-C measures/subject (altitude measures)	4.2	2.4	1	10

AMS (%) is based on subjects that were sick on at least one measurement occasion during their altitude exposure.
Min, minimum; max, maximum.

individuals were at altitudes >3500 m. All volunteers were fit, healthy, and relatively young. All received medical examinations, and none had any preexisting medical condition that warranted exclusion from participation. Each gave written and verbal acknowledgment of their informed consent and was made aware of their right to withdraw without prejudice at any time. The studies were approved by the Institutional Review Board of the USARIEM in Natick, MA. Investigators adhered to the policies for protection of human subjects as prescribed in Army Regulation 70–25, and the research was conducted in adherence with the provisions of 32 CFR Part 219.

Dependent variables. AMS was assessed at various time points depending on the protocol for each study. In addition to a baseline measurement of AMS at sea level, a minimum of one measurement and a maximum of ten repeated measurements of AMS were made per individual at altitude to delineate the time course of AMS. Given that AMS does not typically develop until 4–6 h of altitude exposure (10,28), only time points greater than 4 h were considered in the severity, prevalence, and grade of severity models. The severity of AMS was determined from information gathered using the Environmental Symptoms Questionnaire (ESQ-III) (32) or shortened version of the ESQ-III (4). The AMS-C scores were log transformed for data analysis to conform to normality assumptions, and zero scores for AMS-C were assigned a random value between 0.01 and 0.10 to perform the log transformation. The prevalence of AMS was determined using a weighted AMS cerebral factor score (AMS-C) where a value ≥0.7 indicated the presence of AMS. AMS was also broken down into severity categories by cutoff scores partially established in the ESQ (32). These categories were defined as follows: 1) mild AMS, ≥0.7 and <1.530; 2) moderate AMS, ≥1.530 and <2.630; and 3) severe AMS: ≥2.630.

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Independent variables. Altitude coded in kilometers (i.e., one unit increase in altitude was equivalent to a 1000-m increase in altitude), time coded in 24-h increments (one unit increase in time was equivalent to 24 h), physical activity level (low and high), and sex (men and women) were entered as major predictor variables in the model. The following covariates were also included in the model: age, body mass index (BMI) (weight/height^2), race (white and all others), and smoking status (current smoker or >3 months nonsmoker).

Statistical analysis. We modeled AMS using individual growth models containing subject-specific intercepts and slopes for AMS severity, prevalence, and grade of severity over time at altitude using PROC MIXED and PROC GLIMMIX (SAS 9.1, Cary, NC) (34). General linear and logistic mixed models allow the intercepts and slopes to vary by individuals such that individual predictions of AMS can be calculated for subjects in the data set (16,35). These models can accommodate repeated-measures data, missing data over time, irregularly spaced measurements, and unbalanced data and can easily handle both time-varying and time-invariant covariates (16,35). For the AMS grade of severity model (i.e., mild, moderate, and severe), we used a proportional odds model with different intercepts for adjacent categories.

Unconditional means models (i.e., with no predictors) were initially fit for AMS-C scores to evaluate whether significant variation in the data warranted inclusion of predictor variables. An unconditional growth model for the pattern of change in AMS-C over time (i.e., linear vs quadratic vs cubic) was assessed by regressing time, time^2, and time^3 on AMS-C in turn as both fixed and random effects. If higher orders of time were not significant ($P < 0.05$), they were dropped from the model as both a fixed and random effect and the model was rerun. Time was centered at 20 h of exposure for ease of interpretation of intercepts. After determining a suitable parsimonious individual growth model, all level 2 covariates and their interactions with time and each other were included in the model. Nonsignificant covariates ($P > 0.10$) and their interactions with time and each other were eliminated from the model one at a time starting with the least significant effect until the final model was determined. Statistical significance was set at $P < 0.05$.

Model diagnostics for general linear and logistic mixed models were performed to compare the data with the fitted models to highlight any discrepancies. Diagnostic tools included residual analysis, outlier detection, influence analysis, and model assumption verification. There were no systematic trends in the residuals that indicated a misspecified model. Twenty-one subjects had AMS-C scores that were potential outliers, but after careful inspection, it was determined that the data were not erroneous. The distribution of the random effects for intercept, time, and time^2 were all normally distributed assessed by skewness and kurtosis statistics. Internal validation of both models was conducted using Efron bootstrap resampling with replacement on 1000 bootstrap samples (9). The difference between the root mean square error for the AMS severity model and root mean square error for the 1000 bootstrap samples was small and within the measurement error of the ESQ. The percent correct classification of sick versus not sick in the AMS prevalence model was 95.2% in the original model and 90.1% for the mean of the 1000 bootstrap samples

TABLE 2. Parameter estimates and SE from fitting a taxonomy of multilevel models examining changes in AMS cerebral factor (AMS-C) scores over the first 48 h of exposure to various altitudes.

	Model A Unconditional Means	Model B Unconditional Growth	Model C (Altitude)	Model D (Altitude/Activity/Sex)
Fixed effects				
Intercept	−1.32 (0.06)**	−0.26 (0.09)*	−4.07 (0.42)**	−4.55 (0.49)**
CTime		0.28 (0.08)**	−0.31 (0.44)	−0.66 (0.55)
CTime^2		−2.75 (0.15)**	1.51 (0.74)*	1.82 (0.91)*
Altitude			0.98 (0.11)**	1.03 (0.11)**
Altitude × CTime			0.14 (0.11)	0.18 (0.12)
Altitude × CTime^2			−1.10 (0.19)**	−1.11 (0.19)**
Activity				0.09 (0.17)*
Activity × CTime				0.37 (0.18)*
Activity × CTime^2				0.55 (0.34)
Sex				0.33 (0.18)
Sex × CTime				−0.16 (0.17)
Sex × CTime^2				−0.94 (0.32)*
Variance components				
Within person	1.55 (0.08)**	0.71 (0.04)**	0.71 (0.04)**	0.71 (0.04)**
Intercept	0.61 (0.07)**	1.57 (0.18)**	1.05 (0.14)**	1.04 (0.13)**
Time		0.56 (0.12)**	0.55 (0.12)**	0.54 (0.11)**
Time^2		2.62 (0.58)**	1.85 (0.49)**	1.75 (0.47)**
Goodness-of-fit statistics				
$R^2 y\hat{y}$		0.25	0.34	0.37
AIC	4523	3794	3730	3722

Time was centered (CTime) at 20 h of altitude exposure.
Example computation of an AMS-C score in the final model is as follows for high active (activity = 1) male (sex = 1) at 4500 m (altitude = 4.5) at 20 h of exposure (CTime = 0): AMS-C = $e^{(-4.55 + (1.03 \times 4.5) + (0.09 \times 1) + (0.33 \times 1))}$ = 1.66. The parameter estimates are per 24-h increase in time and 1000-m increase in altitude, and the reference category for sex is female and activity is low active. The intercept represents the value for an inactive female at 20 h of exposure and 0-m altitude.
* $P < 0.05$.
** $P < 0.001$.
$R^2 y\hat{y}$, correlation $(y\hat{y})^2$; AIC, Akaike Information Criteria.

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when the cutoff value for the predicted probability was set at >50%.

RESULTS

Table 2 presents the parameter estimates of fitting a taxonomy of multilevel models for change to the AMS-C severity data starting with the unconditional means model (model A); unconditional growth model with intercept, time, and time^2 (model B); individual growth model with one predictor (i.e., altitude) (model C); and the final individual growth model with three predictors (i.e., altitude, activity, and sex) (model D). This equation for the final AMS model (model D) predicts that AMS severity increases approximately twofold ($[e^{1.026} - 1]100 = 179\%$) for every 1000-m increase in altitude at 20 h regardless of activity or sex. The absolute increase in AMS severity for every 1000-m increase in altitude is nonlinear because a twofold increase is based on the initial AMS severity scores, which start at a lower level at 2500 m (0.21) compared with 3500 m (0.59). For instance, the predicted AMS-C score in a high active man increases 0.38 going from 2500 to 3500 m ($[0.21 \times 1.79] + 0.21 = 0.59$) but increases 1.06 going from 3500 to 4500 m ($[0.59 \times 1.79] + 0.59 = 1.65$).

Figure 1 presents the population-average predictions for AMS-C severity scores using model D specified in Table 2.

This figure delineates the time course of AMS severity and demonstrates that AMS peaks between 18 and 22 h of exposure at all altitudes and decreases to near baseline values by 42–48 h of exposure regardless of altitude, activity level, or sex. This figure clearly shows that men exhibited 38% ($(e^{0.3258} - 1)100$) higher peak AMS severity scores than women regardless of altitude or activity. In addition, this figure demonstrates that high active men and women exhibited similar AMS-C severity scores until 15 h of exposure. After 15 h of exposure, high active men and women diverged from the low active men and women and demonstrated higher peak AMS severity scores at 20 h of exposure that took approximately 3–4 h longer to resolve than their low active counterparts.

Table 3 presents the parameter estimates for both the AMS prevalence (i.e., sick vs not sick) and grade of severity (i.e., mild, moderate, and severe) models. These equations predict the AMS prevalence and grade of severity at any altitude between 2000 and 4500 m and 4 and 48 h of exposure. The equation for AMS prevalence predicts that the odds (odds ratio (OR), 5.43; confidence interval (CI), 3.24–9.10) of experiencing AMS increases approximately 4.5-fold for every 1000-m increase in altitude at 20 h of exposure, whereas the grade of severity model predicts that the odds of being in a higher ordered category of AMS (OR, 6.204; CI, 3.54–10.88) increases approximately fivefold
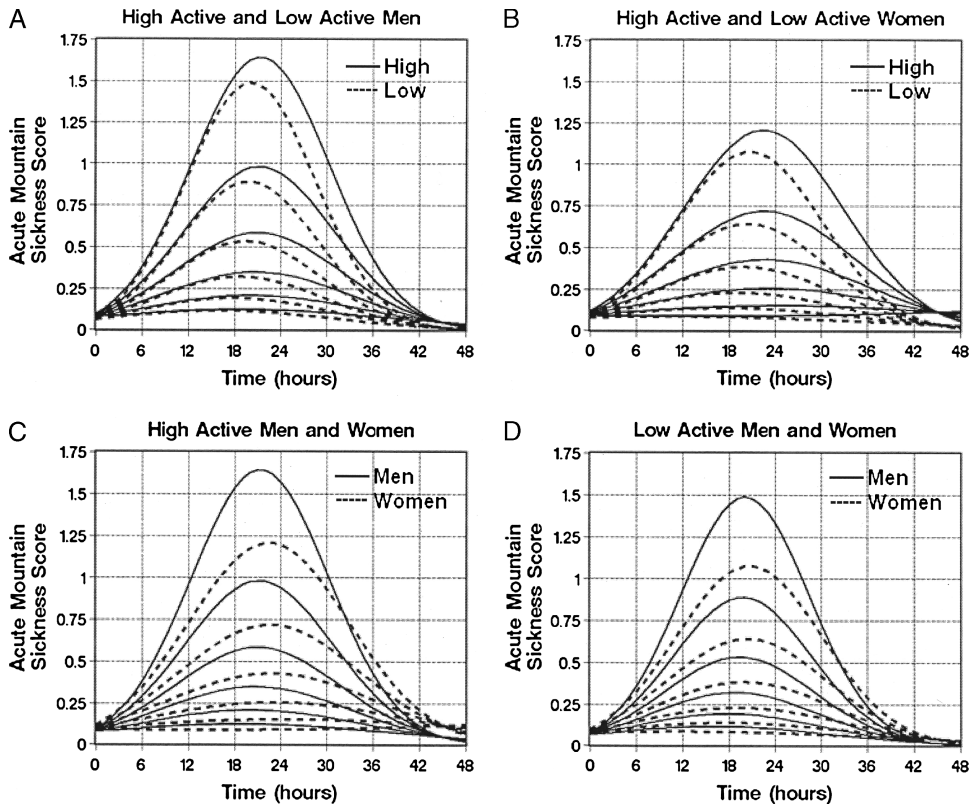

FIGURE 1—This figure demonstrates predictions of AMS severity scores over the first 48 h of altitude exposure after rapid ascent to altitudes ranging from 2000 to 4500 m. The lowest group of lines starts at 2000 m and increases by 500 m until reaching 4500 m for the top group of lines. Panels A and B demonstrate the effect of activity on AMS scores in high active versus low active men and high active versus low active women. Panels C and D represent the effect of sex on AMS scores in high active men and women and low active men and women.

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TABLE 3. Parameter estimates and SE from the logistic mixed-effects regression model of AMS prevalence (i.e., sick vs not sick) and grade of severity (i.e., mild, moderate, and severe) outcome measures over time at altitude.

Variable	AMS Prevalence Model Parameter Estimates and SE	AMS Grade of Severity Model Parameter Estimates and SE
Intercept (binary)	−7.04 (1.15)**	
Intercept 3		−10.66 (1.27)**
Intercept 2		−9.04 (1.26)**
Intercept 1		−7.46 (1.25)**
CTime	−4.11 (1.74)*	−3.79 (1.85)*
CTime^2	−2.74 (0.54)**	−3.03 (0.52)**
Altitude	1.69 (0.26)**	1.82 (0.28)**
Altitude × CTime	1.07 (0.39)**	0.93 (0.42)*
Activity	0.54 (0.29)*	0.55 (0.31)
Activity × CTime	0.39 (0.38)	0.39 (0.38)
Sex	0.50 (0.34)*	0.57 (0.34)
Sex × CTime	0.21 (0.33)	0.22 (0.35)
Sex × CTime^2	−1.29 (0.68)*	−1.66 (0.65)*

Time was centered (CTime) at 20 h of altitude exposure. There is only one intercept for the binary outcome model but three intercepts for the ordinal outcome model. The ordinal AMS prevalence model is modeling the probability of being in a higher ordered category of AMS. The probability of AMS from the binary or ordinal model is calculated using the following formula: AMS (%) = e^{logit} / 1 + e^{logit} . An example calculation of the logit using the binary equation for a high active (activity = 1) male (sex = 1) at 4500 m (altitude = 4.5) at 20 h of exposure (CTime = 0) is logit = (−7.04 + (1.69 × 4.5) + (0.54 × 1) + (0.50 × 1)). In this case, the logit = 1.609 and the AMS probability ($e^{1.609}$ / 1 + $e^{1.609}$) equals 83.4%. The ordinal logit can be calculated using the ordinal equation for the probability of severe AMS using intercept 3, severe plus moderate AMS using intercept 2, and severe plus moderate plus mild AMS using intercept 1. The parameter estimates are per 24-h increase in time and 1000-m increase in altitude, and the reference category for sex is female and activity is low active. The intercept represents the value for an inactive female at 20 h of exposure at 0 m.
* $P < 0.05$.
** $P < 0.001$.

for every 1000-m increase in altitude regardless of activity or sex.

Figure 2 presents the population-average predictions for the prevalence of AMS in four different subgroups using the parameter estimates contained in Table 3. The figure delineates the time course of AMS prevalence and demonstrates that AMS prevalence peaks between 16 and 24 h of exposure and is reduced to near baseline values by 48 h of exposure at all altitudes except 4500 m. This figure also demonstrates that high active men and women demonstrate a 72% increase in the odds (OR, 1.72; CI, 1.03–3.08) of AMS compared with low active men and women regardless of altitude or sex at 20 h of exposure. Although men demonstrated a tendency ($P = 0.10$) for increased odds of AMS (OR, 1.65; CI, 0.84–3.25), the sex effect for AMS prevalence was not significant.

Figure 3 presents the population-average predictions for the prevalence of mild, moderate, severe, and total AMS at 20 h of exposure at six different altitudes (i.e., 2000, 2500, 3000, 3500, 4000, and 4500 m) in four subgroups of the population. The results from the grade of AMS severity model are the following: 1) high active men and women demonstrated a 73% increase in the odds (OR, 1.73; CI, 1.03–3.21) of being in a higher ordered category of AMS at 20 h regardless of altitude or sex, and 2) men demonstrated a tendency ($P = 0.10$) for increased odds (OR, 1.77; CI, 0.89–3.49) of being in a higher ordered category of AMS at 20 h of exposure. Fifty-one of 308 individuals experienced severe AMS (16.56%), and all but one of those subjects were

above 4000 m. Written equations (see Table, Supplemental Digital Content 1, http://links.lww.com/MSS/A230 which illustrates how to calculate AMS severity, prevalence, and grade of severity) provide easy-to-follow instructions for the user community to calculate AMS over a wide range of altitudes and time points in both sexes for low and high activity groups.

DISCUSSION

This article presents the first predictive models of AMS severity, prevalence, and grade of severity after rapid ascent and stay over a wide range of fixed altitudes during the first 48 h of exposure in unacclimatized lowlanders. These AMS models quantify the increased risk of AMS for a given gain in elevation, delineate the time course of AMS, and define the baseline demographics and physiologic descriptors that increase the risk of AMS. In addition, these models provide estimates of the different grades of AMS severity (i.e., mild, moderate, and severe), which is vital information for medical planners given that mild AMS is a mere nuisance, whereas severe AMS can turn into a life-threatening situation (7,28). Lastly, these AMS models are unique compared with previous models because they do not require previous exposure to altitude to calculate the predicted risk of AMS. The models contained in this article can be used to predict AMS before exposure to a wide range of altitudes in any unacclimatized lowlander just by knowing the destination altitude, length of stay at altitude, physical activities planned during the stay at altitude, and general baseline demographics.

The major predictive factors for estimating AMS severity, prevalence, and grade of severity in these models are altitude, time at altitude, physical activity level, and sex. Altitude was the most significant factor in the models. Previous research has already demonstrated a dose/response relationship between increased altitude and increased AMS severity and prevalence (17,20,21), but available estimates are general and lack precision. For instance, previous guidance suggests an 18%–40% prevalence of AMS between 2000 and 3000 m (7,23). The ability to provide pinpoint estimates of both AMS severity and prevalence using an equation at *any* given altitude and quantify the increased risk of AMS for a given gain in elevation represents a significant advancement in the field. For instance, for every 1000-m gain in elevations, these models predict that AMS severity increases approximately twofold, the odds of experiencing AMS increases approximately 4.5-fold, and the probability of falling into a higher ordered category of AMS increases approximately fivefold.

The second most significant factor in these AMS models was time at altitude. These models delineate the time course of AMS over a wide range of altitudes, and this time course has not been previously defined using a mathematical model. Previous AMS models typically examined one time point and one altitude and provided no information on when AMS symptoms peak and recover (21,22,37,39). Estimates of
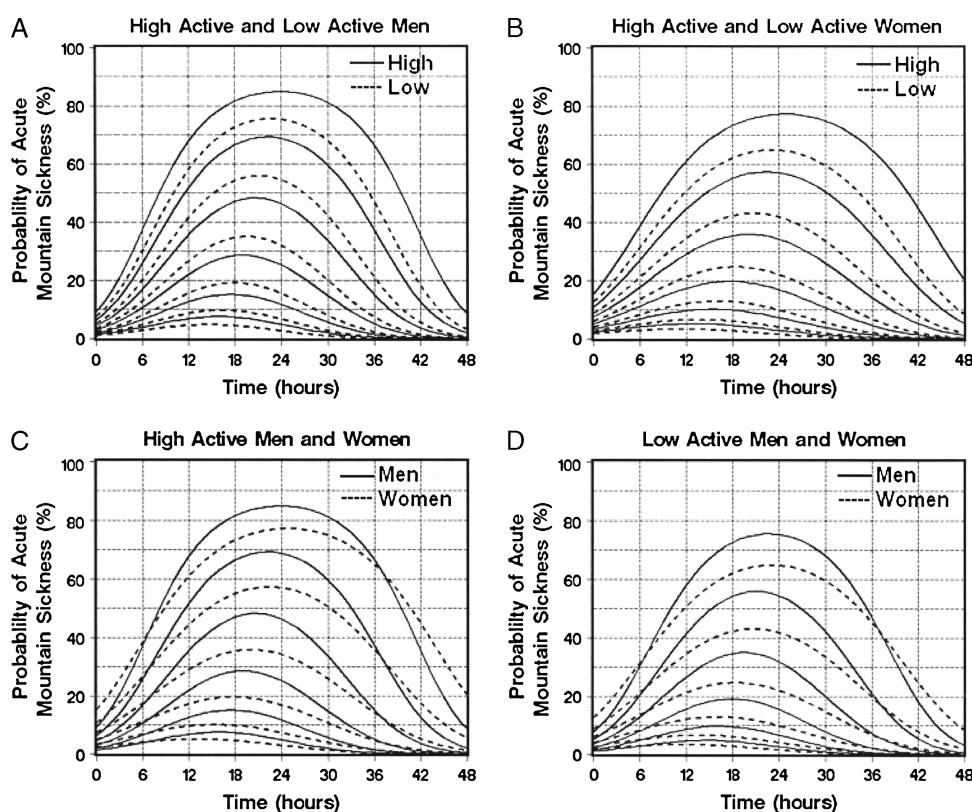
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FIGURE 2—This figure demonstrates predictions for the probability of AMS over the first 48 h of altitude exposure after rapid ascent to altitudes ranging from 2000 to 4500 m. The lowest group of lines starts at 2000 m and increases by 500 m until reaching 4500 m for the top group of lines. Panels A and B demonstrate the effect of activity on probability of AMS in high active versus low active men and high active versus low active women. Panels C and D demonstrate the effect of sex on probability of AMS in high active men versus high active women and low active men versus low active women.

AMS at differing time points other than after the first night at altitude are important when planning both short-term (i.e., 6–12 h) and long-term (i.e., 24–48 h) military missions, recreational activities, and search and rescue operations. Our models predict that AMS peaks after 16–24 h of altitude exposure and resolves by 48 h of exposure except at 4500 m. This finding disagrees with general guidance provided in the literature, suggesting that AMS peaks within 24–48 h of altitude exposure and resolves over the next 3–7 d (1,10). Our models predict that AMS peaks sooner and resolves earlier than previously suggested. As individuals ascend around 8 a.m. to 12 noon, predictions from our model would indicate that AMS peaks by 5–9 a.m. the next morning and resolves the following morning at a given altitude if no further ascent occurs. This guidance holds for the lower altitudes (<4000 m), but as individual ascend to higher altitudes (i.e., 4500 m), the prevalence of AMS remains increased after 48 h of exposure. For higher elevations, resolution of AMS symptoms may take another day or two of acclimatization.

Physical activity was the third most significant factor in the AMS models. High physical activity has been shown to increase the prevalence of AMS within the first 10 h of exposure to approximately 4500 m most likely because of reductions in arterial oxygen saturation and alterations in fluid balance during exercise (2,30). Increased exertion during ascent to altitude in trekkers and mountaineers has also been shown to increase the risk of developing AMS (5,21). The degree of increase in this risk, however, has never been quantified. Our model demonstrates that high active men and women demonstrated a 72% increase in the odds of AMS and 73% increase in the proportional odds of falling into a higher ordered category of AMS regardless of sex or altitude. Although AMS-C scores did not differ between high and low active men and women until 15 h of exposure, peak AMS-C scores were elevated in high compared with low active men and women at 20 h of exposure. In addition, high active men and women took approximately 3–4 h longer to resolve AMS than low active men and women. Our model, therefore, agrees with previous guidance suggesting limited activity in the first 24 h at altitude, if possible, to decrease the risk of experiencing AMS (7).

The relationship between sex and the risk of AMS has been reported in numerous studies on trekkers and mountaineers (12,18,20,37,39). Most studies have reported that men and women are equally susceptible to AMS (12,20,21,33,39) or that women have a slightly greater risk of developing AMS (18,37), but these studies only examined the prevalence of AMS. We found that women demonstrated 29% lower ($P = 0.05$) AMS severity scores at

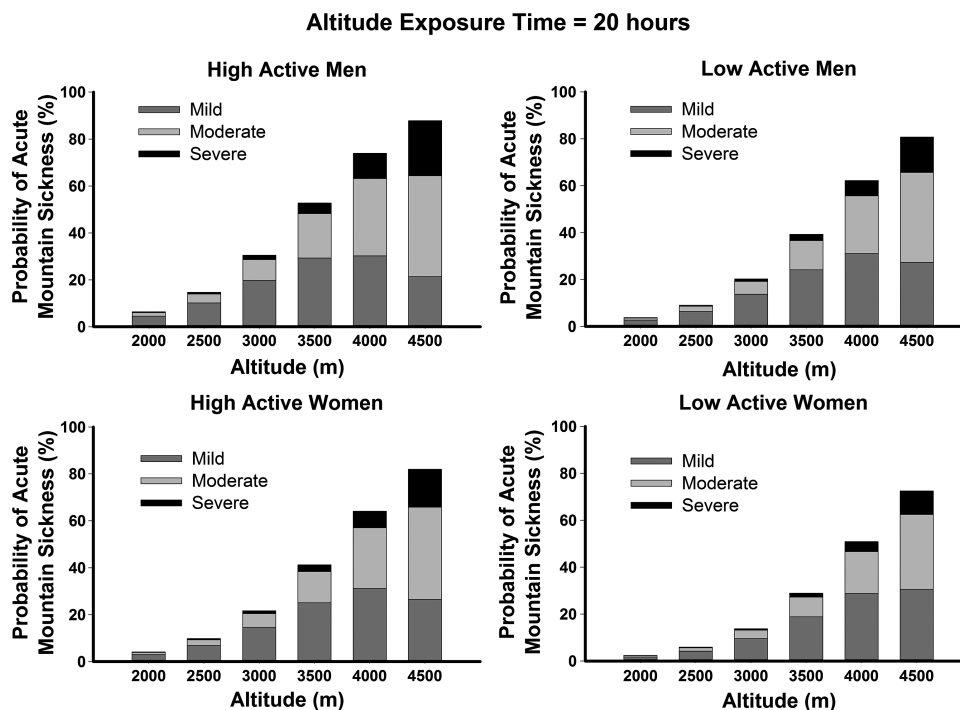**Altitude Exposure Time = 20 hours**

FIGURE 3—This figure demonstrates the probability of mild, moderate, and severe AMS going from 2000 to 4500 m in high active men, low active men, high active women, and low active women.

20 h regardless of altitude or activity level, which agrees with one previous report (14). The odds of experiencing AMS and odds of falling into a higher ordered category of AMS also tended ($P = 0.10$) to be lower in women compared with men. Therefore, our models found that the severity but not the prevalence of AMS was higher in men. This finding may be because all of our women in our database were premenopausal and progesterone, a known ventilatory stimulant, is higher in women compared with men (8,40). An increase in ventilation is an important aspect of altitude acclimatization and has been associated with a reduction in AMS (3,36). Although a few studies found increased ventilation in acclimatized women compared with men (6,14), more recent work has not substantiated this finding in unacclimatized women (24). Other physiologic differences between men and women (i.e., differences in endothelial permeability, free radical production, or types of symptoms) may be contributing to this sex difference in AMS symptom severity (15,19), but more work is needed to elucidate potential physiologic mechanisms.

The proportional odds model demonstrates that the proportion of severe cases of AMS, which is the category that would require evacuation or immediate medical attention, increases significantly (i.e., 10%–20%) around 4000 m, depending on the subgroup examined. This prediction agrees closely with the percentage of reported evacuations (14.6%) due to severe altitude illness during current military operations in Afghanistan (25). This type of information provides a critical medical planning tool for clinicians, health care workers, and military leaders advising personnel rapidly ascending to high mountainous regions because

operational plans can be altered if the risk of ascending to a higher elevation outweighs the benefit. If plans or mission cannot be altered, as often occurs in the military, the degree of increased risk associated with ascending to a higher elevation will at least be well understood (31).

The fact that age, BMI, race, and smoking status were not significant factors in predicting AMS severity, prevalence, or grade of severity is consistent with many previous reports (18,21,22,33,37). Although some (12,39) have reported a decreased prevalence of AMS with increasing age and lower BMI, these conclusions were based on older (age ≥50 yr) and obese individuals (BMI ≥30 kg·m^{-2}). Others have reported a curvilinear relationship between age and AMS, indicating that the protective effect of age is greatest from youth to young adult (38,42). We did not have any youth or older individuals in our data set, which may have limited age as a significant predictor of AMS. A greater nocturnal desaturation in obese individuals at altitude has been associated with a greater prevalence of AMS (27), and heavier individuals were reportedly more likely to develop AMS at altitude (11). Our data set was limited to relatively fit individuals between 18 and 45 yr with a mean age of approximately 24 yr. We cannot, therefore, exclude the possibility that age or obesity may have been a factor in our model had we used older or obese individuals in our data set. Although conclusions from this model suggest that race is not a significant factor for the development of AMS within the broad classification categories used in the model (i.e., white and nonwhite), this factor requires further study because of the limited number of nonwhite individuals in our database.

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Limitations of the study should be acknowledged. First, the age range is limited to 18–45 yr. Therefore, age effects on AMS occurring below 18 yr and above 45 yr cannot be detected. Second, the number of women in the database was limited (approximately 23%) even though the distribution was equally spread across altitudes and age groups. This fact may have contributed to the lack of significance in the prevalence of AMS between men and women when severity was increased in men. Third, previous history of AMS was not included as a factor in these models. Prior AMS susceptibility has been shown to be an important predictor of future AMS (26,33). Given the small number of volunteers with a previous history of AMS in our database (i.e., eight volunteers), our conclusions are limited to individuals with no previous altitude experience. Last, although these models represent a significant advancement in the field, the total explained outcome variation in AMS-C scores is 35.5%. This suggests the need for additional predictors of AMS in the models. Basic blood parameters (i.e., hemoglobin, hematocrit), fitness levels (i.e., maximal oxygen uptake), physiologic variables (i.e., arterial oxygen saturation, heart rate), and genomic, proteomic, and metabolomic markers of hypoxic stress will add to the predictive ability of these models in the future.

CONCLUSIONS

In conclusion, these models provide the first quantifiable estimates of AMS risk over a wide range of altitudes and time points. The results suggest that in addition to altitude and time spent at altitude, high activity increases the risk of developing AMS. The AMS models also suggest that AMS severity but not prevalence is increased in men. Although predictions from these models are limited to a homogeneous population that is relatively young and fit, these AMS models quantify the increased risk of AMS for a given gain in elevation, delineate the time course of AMS, define the baseline demographics and physiologic factors that increase the risk of AMS, and provide estimates of different grades of AMS severity (i.e., mild, moderate, and severe). These AMS models are unique in that they can predict AMS before exposure to a wide range of altitudes in unacclimatized lowlanders after rapid ascent just by knowing the destination altitude, length of stay at altitude, physical activities planned during the stay at altitude, and general baseline demographics. Clinicians, health care providers, and military commanders can use estimates provided by these models as a medical planning tool to prevent and/or effectively manage AMS in the millions of people exposed annually to high mountainous terrain.

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